Refs ordered 9/11.

Welcome to DIALOG
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Last logoff: 10apr95 15:34:40
Logon file405 11apr95 09:48:15
? b 411
File 411:DIALINDEX(R)

DIALINDEX(R)

? set files biochem

You have 21 files in your file list.
(To see banners, use SHOW FILES command)
? s flt or flk

Your SELECT statement is:
s flt or flk

Items	File
233	5: BIOSIS PREVIEWS(R)_1969-1995/Mar W3
133	73: EMBASE_1974-1995/Iss 13
93	76: Life Sciences Collection_1978-1995/Feb
1	125: CLAIMS(R)/US PATENT_Feb 1995/Mar 28
52	144: Pascal_1973-1994/Aug
161	155: MEDLINE(R)_1966-1995/May W4
17	156: TOXLINE(R)_1965-1995/Mar
18	340: CLAIMS(R)/US PATENTS ABS_1950-1995/JAN
1	348: European Patents_1978-1995/Apr W1
8	350: Derwent World Pat._1963-1980/UD=9512
36	351: DERWENT WPI_1981-1995/UD=9512;UA=9508;UM=9504
26	357: Derwent Biotechnology Abs_1982-1995/Apr B2
4	358: Current Biotech Abs_1983-1995/Apr
55	377: Derwent Drug File_1983-1995/Jan W1
73	399: CA SEARCH(R)_1967-1995/UD=12214
143	434: SciSearch(R)_1974-1995/Mar W3
1	442: AMA Journals Online_1982-1995/Feb
2	444: NEJM Online_1985-1995/Apr W1

18 files have one or more items; file list includes 21 files.
? s flt3 or flk2

Your SELECT statement is:
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Items	File
49	5: BIOSIS PREVIEWS(R)_1969-1995/Mar W3
26	73: EMBASE_1974-1995/Iss 13
14	76: Life Sciences Collection_1978-1995/Feb
14	144: Pascal_1973-1994/Aug
28	155: MEDLINE(R)_1966-1995/May W4

1 156: TOXLINE(R)_1965-1995/Mar
1 348: European Patents_1978-1995/Apr W1
3 351: DERWENT WPI_1981-1995/UD=9512;UA=9508;UM=9504 3 357: Derwent Biotechnology Abs_1982-1995/Apr B2 20 399: CA SEARCH(R)_1967-1995/UD=12214
50 434: SciSearch(R)_1974-1995/Mar W3
1 442: AMA Journals Online_1982-1995/Feb

12 files have one or more items; file list includes 21 files.
? rf

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Ref	Items	File
N1	50	434: SciSearch(R)_1974-1995/Mar W3
N2	49	5: BIOSIS PREVIEWS(R)_1969-1995/Mar W3
N3	28	155: MEDLINE(R)_1966-1995/May W4
N4	26	73: EMBASE_1974-1995/Iss 13
N5	20	399: CA SEARCH(R)_1967-1995/UD=12214
N6	14	76: Life Sciences Collection_1978-1995/Feb
N7	14	144: Pascal_1973-1994/Aug
N8	3	351: DERWENT WPI_1981-1995/UD=9512;UA=9508;UM=9504
N9	3	357: Derwent Biotechnology Abs_1982-1995/Apr B2
N10	1	156: TOXLINE(R)_1965-1995/Mar

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11apr95 09:51:50 User217743 Session D308.2
$1.50 0.050 Hrs File411
$1.50 Estimated cost File411
$1.50 Estimated cost this search
$1.50 Estimated total session cost 0.083 Hrs.

SYSTEM:OS - DIALOG OneSearch
File 155:MEDLINE(R) 1966-1995/May W4
(c) format only 1995 Knight-Ridder Info
*File 155: The annual reload is now available.
File 434:SciSearch(R) 1974-1995/Mar W3
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Set	Items	Description

? s (flt()3 or flk()2 or flt3 or flk2)

Processing
201 FLT

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      3878672  3
         18  FLT(W)3
        171  FLK
      4744895  2
         28  FLK(W)2
         78  FLT3
         29  FLK2
   S1    113  (FLT()3 OR FLK()2 OR FLT3 OR FLK2)
? s s1 and ligand

        113  S1
      97504  LIGAND
   S2     63  S1 AND LIGAND
? rd

>>>Duplicate detection is not supported for File 351.

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...completed examining records
   S3     50  RD (unique items)
? t s3/3,ab/all


 3/3,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 1995 Knight-Ridder Info. All rts. reserv.

09225405   95155405
  Identification and characterization of a functional murine *FLT3* isoform produced by exon skipping.
  Lavagna C; Marchetto S; Birnbaum D; Rosnet O
  Laboratoire d'Oncologie Moleculaire, INSERM U.119, Marseille, France.  J Biol Chem (UNITED
STATES)  Feb 17 1995,  270 (7) p3165-71,  ISSN 0021-9258  Journal Code: HIV
  Languages: ENGLISH
  Document type: JOURNAL ARTICLE
  The *FLT3* gene encodes an hematopoietic receptor related to the receptors for
colony-stimulating factor 1, FMS, and for Steel factor, KIT. The extracellular part of these molecules is
exclusively composed of five immunoglobulin (Ig)-like domains, designated 1 to 5, from the amino
terminus to the carboxyl terminus of the extracellular region. We have isolated a unique murine
*FLT3* cDNA that codes for a variant isoform of *FLT3* , devoid of the fifth Ig-like domain, by
comparison with the prototypic form. The corresponding mRNA is the result of a splicing event that
leads to the elimination of two coding exons. mRNA coding for this variant was detected in almost
all the tissues expressing the mRNA coding for the prototypic molecule, although at a lower level.
*Ligand*-induced tyrosine phosphorylation of the two isoforms was equivalent in COS-1 transfected
cells, indicating that the fifth Ig-like domain is not strictly necessary for either *ligand*-binding or kinase
activation.

 3/3,AB/2     (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 1995 Knight-Ridder Info. All rts. reserv.
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09222074 95152074
FLK-*2*/*FLT*-*3* *ligand* regulates the growth of early myeloid progenitors isolated from human fetal liver.
Muench MO; Roncarolo MG; Menon S; Xu Y; Kastelein R; Zurawski S; Hannum CH; Culpepper J; Lee F; Namikawa R
Human Immunology and Molecular Biology Departments, DNAX Research Institute, Palo Alto, CA.
Blood (UNITED STATES) Feb 15 1995, 85 (4) p963-72, ISSN 0006-4971 Journal Code: A8G
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The effects of the recently identified *FLK*-*2*/*FLT*-*3* *ligand* (FL) on the growth of purified human fetal liver progenitors were investigated under serum-deprived culture conditions. FL alone was found to stimulate modest proliferation in short-term cultures of CD34++ CD38+ lineage (Lin)-light-density fetal liver (LDFL) cells and the more primitive CD34++ CD38- Lin- LDFL cells. However, the low levels of growth induced by FL were insufficient for colony formation in clonal cultures. Synergism between FL and either granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-3 (IL-3) or KIT *ligand* (KL) was observed in promoting the growth of high-proliferative potential (HPP) colony-forming cells (CF) and/or low-proliferative potential (LPP)-CFC in cultures of CD34++ CD38+ Lin- and CD34++ CD38- Lin- LDFL-cells. FL, alone or in combination with other cytokines, was not found to affect the growth of CD34+ Lin- LDFL cells, the most mature subpopulation of fetal liver progenitors investigated. The growth of the most primitive subset of progenitors studied, CD34++ CD38- Lin- LDFL cells, required the interactions of at least two cytokines, because only very low levels of growth were observed in response to either FL, GM-CSF, IL-3 or KL alone. However, the results of delayed cytokine-addition experiments suggested that individually these cytokines did promote the survival of this early population of progenitors. Although two-factor combinations of FL, KL, and GM-CSF were observed to promote the growth of early progenitors in a synergistic manner, neither of these factors was found to make fetal liver progenitors more responsive to suboptimal concentrations of a second cytokine. Only myeloid cells were recovered from liquid cultures of CD34++ CD38- Lin- LDFL cells grown in the presence of combinations of FL, KL, and GM-CSF. These results indicate that FL is part of a network of growth factors that regulate the growth and survival of early hematopoietic progenitors.

3/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09194710 95124710
Identification of soluble and membrane-bound isoforms of the murine *flt3* *ligand* generated by alternative splicing of mRNAs. Lyman SD; James L; Escobar S; Downey H; de Vries P; Brasel K; Stocking K; Beckmann MP; Copeland NG; Cleveland LS; et al
Immunex Research and Development Corporation, Seattle, Washington 98101. Oncogene (ENGLAND) Jan 5 1995, 10 (1) p149-57, ISSN 0950-9232 Journal Code: ONC
Contract/Grant No.: N01-CO-74101, CO, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We have recently described a novel hematopoietic growth factor, referred to as the *flt3* *ligand* , that stimulates the proliferation of sub-populations of hematopoietic cells that are enriched for stem and progenitor cells. This factor is a transmembrane protein that undergoes proteolytic cleavage to generate a soluble form of the protein. We have isolated additional *flt3* *ligand*

isoforms by PCR that contain an extra exon and encode what are predicted to be either a soluble form of the *ligand* or a longer version of the transmembrane protein. We have also isolated cDNAs from murine T cell libraries that encode an isoform of the *flt3* *ligand* that has an unusual C-terminus. This isoform results from a failure to splice out an intron during mRNA processing. The protein encoded by this cDNA is expressed on the cell surface, where it is biologically active. However, this novel isoform does not appear to give rise to a soluble form of the protein. Regulation of mRNA splicing is likely to control the generation of cell bound or soluble forms of this hematopoietic growth factor. Genetic mapping studies localize the gene encoding the *flt3* *ligand* to the proximal portion of mouse chromosome 7 and to human chromosome 19q13.3.

3/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09073966 95003966
Analysis of the mitogenic pathway of the *FLT3* receptor and characterization in its C terminal region of a specific binding site for the PI3' kinase.
Casteran N; Rottapel R; Beslu N; Lecocq E; Birnbaum D; Dubreuil P Molecular and Functional Hematology Laboratory, Unite 119, INSERM, Marseille, France.
Cell Mol Biol (Noisy-le-grand) (FRANCE) May 1994, 40 (3) p443-56, Journal Code: BNA
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The *FLT3* receptor tyrosine kinase (RTK) belongs to the class III subfamily which includes PDGF, CSF1 and SLF receptors. The recent cloning of the *FLT3* *ligand* suggesting its important role in the differentiation and proliferation of the hematopoietic stem cells, has confirmed the initial expression analysis showing restricted pattern of receptor expression within the primitive hematopoietic population. To better understand the function of the *FLT3* receptor and its relationship with the other hematopoietic RTKs, we analyzed the mitogenic pathway and substrate specificity of this receptor. The construction of a chimeric receptor called FF3, between the extracellular region of the CSF1 receptor fused with the transmembrane and the cytoplasmic regions of *FLT3*, has allowed an analysis in the absence of *FLT3* *ligand*. We have shown in previous studies that FF3 is able to transduce the signal induced by CSF1, to induce tyrosine phosphorylation and/or association of several cytoplasmic proteins. We show here that this new receptor is fully functional in Ba/F3 hematopoietic cells, inducing a CSF1 dependence when expressed at the surface of this IL3 dependent cell line. The PI3' Kinase interacts with the FF3 receptor through SH2 domains and its binding site is localized on the tyrosine residue 958 in the C terminal part of the receptor.

3/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09072959 95002959
Cellular and molecular characterization of the role of the *flk*-*2*/ *flt*-*3* receptor tyrosine kinase in hematopoietic stem cells. Zeigler FC; Bennett BD; Jordan CT; Spencer SD; Baumhueter S; Carroll KJ; Hooley J; Bauer K; Matthews W
Department of Molecular Biology, Cell Genetics, Genetech, Inc, South San Francisco, CA.
Blood (UNITED STATES) Oct 15 1994, 84 (8) p2422-30, ISSN 0006-4971 Journal Code: A8G

Languages: ENGLISH
Document type: JOURNAL ARTICLE
The *flk*-*2*/*flt*-*3* receptor tyrosine kinase was cloned from a hematopoietic stem cell population and is considered to play a potential role in the developmental fate of the stem cell. Using antibodies derived against the extracellular domain of the receptor, we show that stem cells from both murine fetal liver and bone marrow can express *flk*-*2*/*flt*- *3* . However, in both these tissues, there are stem cell populations that do not express the receptor. Cell cycle analysis shows that stem cells that do not express the receptor have a greater percentage of the population in G0 when compared with the *flk*-*2*/*flt*-*3* -positive population. Development of agonist antibodies to the receptor shows a proliferative role for the receptor in stem cell populations. Stimulation with an agonist antibody gives rise to an expansion of both myeloid and lymphoid cells and this effect is enhanced by the addition of kit *ligand*. These studies serve to further illustrate the importance of the *flk*-*2*/*flt*-*3* receptor in the regulation of the hematopoietic stem cell.

3/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09010222 94325222
Fms-like tyrosine kinase 3 catalytic domain can transduce a proliferative signal in FDC-P1 cells that is qualitatively similar to the signal delivered by c-Fms.
Rossner MT; McArthur GA; Allen JD; Metcalf D
Walter and Eliza Hall Institute of Medical Research, Royal Melbourne Hospital, Parkville, Victoria, Australia.
Cell Growth Differ (UNITED STATES) May 1994, 5 (5) p549-55, ISSN 1044-9523 Journal Code: AYH
Languages: ENGLISH
Document type: JOURNAL ARTICLE
A full length clone of murine fms-like tyrosine kinase 3 [*flt3*, also known as fetal liver kinase 2 (*flk2*)] was constructed from sequences obtained from a brain complementary DNA (cDNA) library and from cDNA prepared from the cell line Tikaut. In the absence of a *ligand* to study the function of *Flt3*, a chimeric molecule was constructed comprising the extracellular domain of murine c-Fms and the transmembrane and cytoplasmic domains of *Flt3* . A plasmid encoding the chimeric receptor was cotransfected along with a plasmid conferring neomycin resistance into FDC-P1 cells that do not normally express c-fms or *flt3* and require granulocyte-macrophage colony-stimulating factor (GM-CSF) or interleukin 3 for growth. Two types of clones were obtained following selection in GM-CSF and G418. Two of seven clones had the capacity for M-CSF-dependent colony formation in semisolid medium, indicating that the cytoplasmic domain of *Flt3* can transduce a proliferative signal. From the remaining clones, M-CSF-dependent clonogenic cells could be selected by prior bulk liquid culture in M-CSF. It has been shown previously that the GM-CSF-dependent proliferative capacity is strongly inhibited by M-CSF in FDC-P1 cells engineered to express full length c-fms. This phenomenon was also observed with FD/fms-*flt3* cells that were clonogenic in M-CSF. Stimulation of FD/fms or FD/fms-*flt3* cells in liquid culture by M-CSF caused differentiation of a small proportion of cells along the myelomonocytic pathway which was enhanced by the combination of M-CSF and GM-CSF.(ABSTRACT TRUNCATED AT 250 WORDS)

3/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08924756 94239756
Substrate specificities and identification of a putative binding site for PI3K in the carboxy tail of the murine *Flt3* receptor tyrosine kinase. Rottapel R; Turck CW; Casteran N; Liu X; Birnbaum D; Pawson T; Dubreuil P Molecular Hematology Laboratory, Unite 119 INSERM, Marseille, France.
Oncogene (ENGLAND) Jun 1994, 9 (6) p1755-65, ISSN 0950-9232 Journal Code: ONC
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Flt3 is a receptor tyrosine kinase (RTK) structurally related to the CSF-1R encoded by the c-fms locus, Kit and the PDGFR which is restricted in its expression to hematopoietic precursor populations and several distinct cell types within the central nervous system. Although the *ligand* for *Flt3* has recently been identified, the developmental function of *Flt3* within these tissues has not yet been described. In order to examine the signalling properties of this receptor, we previously constructed a chimeric molecule containing the extracellular domain of CSF-1R fused to the transmembrane and cytoplasmic domain of mouse *Flt3* (FF3). The ability of the FF3 to directly associate with or tyrosine phosphorylate specific cytoplasmic signalling molecules in vivo was examined. GAP, Vav, Shc, and to a lesser extent PLC gamma become tyrosine-phosphorylated but no in vivo association with the receptor was detectable. FF3 associates with PI3K activity and the SH2 domains of p85 and Grb-2. Phosphopeptide competition experiments suggest that the PI3K binding site is located outside of the kinase insert in the carboxy tail of the receptor.

3/3,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08920842 94235842
Cloning of the human homologue of the murine *flt3* *ligand*: a growth factor for early hematopoietic progenitor cells.
Lyman SD; James L; Johnson L; Brasel K; de Vries P; Escobar SS; Downey H; Splett RR; Beckmann MP; McKenna HJ
Department of Molecular Genetics, Immunex Research and Development Corp, Seattle, WA 98101.
Blood (UNITED STATES) May 15 1994, 83 (10) p2795-801, ISSN 0006-4971 Journal Code: A8G
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Using a fragment of the murine *flt3* *ligand* as a probe, we have succeeded in cloning a human *flt3* *ligand* from a human T-cell lambda gt10 cDNA library. The human and murine ligands are 72% identical at the amino acid level. Analysis of multiple cDNA clones shows that alternative splicing of the human *flt3* mRNA can occur at a number of positions. A recombinant soluble form of the human *flt3* *ligand* stimulates the proliferation and colony formation of a subpopulation of human bone marrow cells that are CD34+ and are enriched for primitive hematopoietic cells. In addition, the human *flt3* *ligand* also stimulates the proliferation of cells expressing murine *flt3* receptors. Northern blot analysis shows widespread expression of *flt3* *ligand* mRNA transcripts in human tissues.

3/3,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08880428 94195428
Ligand for *FLT3*/*FLK2* receptor tyrosine kinase regulates growth of haematopoietic stem cells

and is encoded by variant RNAs.
Hannum C; Culpepper J; Campbell D; McClanahan T; Zurawski S; Bazan JF; Kastelein R; Hudak S; Wagner J; Mattson J; et al
DNAX Research Institute of Molecular and Cellular Biology, Palo Alto, California 94304-1104.
Nature (ENGLAND) Apr 14 1994, 368 (6472) p643-8, ISSN 0028-0836 Journal Code: NSC
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The *FLT3*/*FLK2* receptor tyrosine kinase is closely related to two receptors, c-Kit and c-Fms, which function with their respective ligands, Kit *ligand* and macrophage colony-stimulating factor to control differentiation of haematopoietic and non-haematopoietic cells. *FLT3*/ *FLK2* is thought to be present on haematopoietic stem cells and found in brain, placenta and testis. We have purified to homogeneity and partially sequenced a soluble form of the *FLT3*/*FLK2* *ligand* produced by mouse thymic stromal cells. We isolated several mouse and human complementary DNAs that encode polypeptides with identical N termini and different C termini. Some variants contain hydrophobic transmembrane segments, suggesting that processing may be required to release soluble *ligand*. The purified *ligand* enhances the response of mouse stem cells and a primitive human progenitor cell population to other growth factors such as interleukins IL-3 and IL-6 and to granulocyte-macrophage colony-stimulating factor, and also stimulates fetal thymocytes.

3/3,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08769791 94084791
Molecular cloning of a *ligand* for the *flt3*/*flk*-*2* tyrosine kinase receptor: a proliferative factor for primitive hematopoietic cells. Lyman SD; James L; Vanden Bos T; de Vries P; Brasel K; Gliniak B; Hollingsworth LT; Picha KS; McKenna HJ; Splett RR; et al
Immunex Research and Development Corporation, Seattle, Washington 98101. Cell (UNITED STATES) Dec 17 1993, 75 (6) p1157-67, ISSN 0092-8674 Journal Code: CQ4
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Cloning of a *ligand* for the murine *flt3*/*flk*-*2* tyrosine kinase receptor was undertaken using a soluble form of the receptor to identify a source of *ligand* . A murine T cell line, P7B-0.3A4, was identified that appeared to express a cell surface *ligand* for this receptor. A cDNA clone was isolated from an expression library prepared from these cells that was capable, when transfected into cells, of conferring binding to a soluble form of the *flt3*/*flk*-*2* receptor. The cDNA for this *ligand* encodes a type I transmembrane protein that stimulates the proliferation of cells transfected with the *flt3*/*flk*-*2* receptor. A soluble form of the *ligand* stimulates the proliferation of defined subpopulations of murine bone marrow and fetal liver cells as well as human bone marrow cells that are highly enriched for hematopoietic stem cells and primitive uncommitted progenitor cells.

3/3,AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08689534 94004534
The expression of cytokine receptors by purified hemopoietic stem cells. Visser JW; Rozemuller H; de Jong MO; Belyavsky A

Institute of Applied Radiobiology and Immunology TNO, Rijswijk, The Netherlands.
Stem Cells (Dayt) (UNITED STATES) Jul 1993, 11 Suppl 2 p49-55, ISSN 1066-5099 Journal Code: BN2
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Sorted fractions from mouse bone marrow containing highly purified hemopoietic stem and progenitor cells were studied for the expression of growth factor receptors. With the use of rhodamine 123 WGA+, 15-1.1-, low density cells were separated into quiescent pluripotent stem cells and committed progenitor cells. RNA was extracted and cDNA was prepared by reverse transcription. Using primers specific for growth factor receptors, the cDNA of each sorted fraction was amplified by polymerase chain reaction (PCR). The quiescent rhodamine 123 dull stem cell fraction was found to express the interleukin 3 (IL-3) receptor beta unit and c-kit, but not the granulocyte-macrophage colony stimulating factor (GM-CSF) receptor beta unit nor *flk*-*2*. The rhodamine 123 bright fraction with activated stem cells and mostly committed progenitor cells similarly expressed the IL-3-R beta, and c-kit. However, this fraction also expressed *flk*-*2* and GM-CSF-R beta. Since the expression of c-kit in the stem cell fraction does not correspond with the poor response to the kit-*ligand* stem cell factor (SCF) by these cells, we further analyzed the fractions with respect to their binding of biotinylated SCF. The SCF-binding cells were found to be all rhodamine 123 bright. This indicates that the expression of c-kit is not sufficient to yield a functional receptor for SCF; c-kit probably needs a partner molecule to form a functional high-affinity binding site for SCF. Similar to the beta unit of the GM-CSF receptor, this partner is then not expressed in the stem cell fraction.(ABSTRACT TRUNCATED AT 250 WORDS)

3/3,AB/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08495405 93205405
Biochemical characterization and analysis of the transforming potential of the *FLT3*/*FLK2* receptor tyrosine kinase.
Maroc N; Rottapel R; Rosnet O; Marchetto S; Lavezzi C; Mannoni P; Birnbaum D; Dubreuil P
Molecular Hematology Laboratory, Unite 119 INSERM, Marseille, France. Oncogene (ENGLAND) Apr 1993, 8 (4) p909-18, ISSN 0950-9232 Journal Code: ONC
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We recently cloned an additional member of the receptor type tyrosine kinase class III. This new gene, called *Flt3* by our group [Rosnet, O., Mattei, M.G., Marchetto, S. & Birnbaum, D. (1991). Genomics, 9, 380-385; Rosnet, O., Marchetto, S., deLapeyriere, O. & Birnbaum, D. (1991). Oncogene, 6, 1641-1650] and *Flk2* by others [Matthews, W., Jordan, C.T., Wieg, G.W., Pardoll, D. & Lemischka, I.R. (1991). Cell, 65, 1143-1152] is strongly related to the important developmental genes Kit, Fms and Pdgfr. The murine 3.2-kb full-length cDNA, when introduced into COS-1 cells, shows the expression of two polypeptides with apparent molecular weights of 155 kDa and 132 kDa. Treatment of cells with N-linked glycosylation inhibitors results in the expression of a 110-kDa protein. We have shown that *FLT3* contains an intrinsic tyrosine kinase activity. A point mutation in a highly conserved residue within the phosphoryltransferase domain inactivates the catalytic function of this receptor, whereas activation by way of a chimeric molecule between the *ligand* -binding domain of colony-stimulating factor type 1 (CSF-1) receptor (CSF-1R) and the kinase domain of *FLT3* results, in the presence of CSF-1, in the development of the transforming activity of this receptor as shown by anchorage-independent cell growth. Finally, expression analysis of the *FLT3* protein shows that, in addition to the hematopoietic system, *FLT3*

is strongly expressed in neural, gonadal, hepatic and placental tissues in the mouse.

3/3,AB/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08495394 93205394
Characterization of the protein encoded by the *flt3* (*flk2*) receptor-like tyrosine kinase gene.
Lyman SD; James L; Zappone J; Sleath PR; Beckmann MP; Bird T Department of Molecular Biology, Immunex Research and Development Corporation, Seattle, Washington 98101.
Oncogene (ENGLAND) Apr 1993, 8 (4) p815-22, ISSN 0950-9232 Journal Code: ONC
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We have developed rabbit polyclonal antibodies to the C-terminus of the *flt3* -encoded protein, which is a member of the receptor tyrosine kinase family. Immunoprecipitation using this antiserum brings down two protein bands, a major band of 143 kDa and a less abundant, more diffuse, band of 158 kDa. Pulse-chase analysis of *flt3* protein from transfected COS-7 cells shows that the larger band is derived from the smaller one and presumably represents maturation of the protein from a glycosylated high-mannose form to a complex carbohydrate form. N-glycosidase F digestion confirmed the presence of N-linked carbohydrates, and cell-surface labeling of *flt3*-transfected cells indicated that the 158-kDa glycoprotein is the species found on the cell surface. A mutated form of the *flt3* protein that was defective in its glycosylational processing was identified. Western blotting of the immunoprecipitated *flt3* protein showed that it is heavily phosphorylated on tyrosine, and that this phosphorylation probably occurs in the absence of *ligand*. In this regard, the *flt3* protein resembles the c-erbB2 protein, which is also highly phosphorylated in the absence of *ligand*. These data suggest that the *flt3* receptor regulates the growth and differentiation of cells via an as yet unknown *ligand*.

3/3,AB/14 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07881834 92019834
Murine *Flt3* , a gene encoding a novel tyrosine kinase receptor of the PDGFR/CSF1R family.
Rosnet O; Marchetto S; deLapeyriere O; Birnbaum D
U. 119 INSERM, Marseille, France.
Oncogene (ENGLAND) Sep 1991, 6 (9) p1641-50, ISSN 0950-9232 Journal Code: ONC
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Receptor-type tyrosine kinases presenting an extracellular region with five immunoglobulin-like domains, and strongly related by sequence similarities in the intracellular region, constitute a family of receptors involved in development and function of various cell lineages. We have isolated and characterized the mouse *Flt3* gene, encoding the sixth member of this family. The *Flt3* gene possesses an open reading frame of 3000 nucleotides, and therefore appears to code for a protein of 1000 amino acids. The deduced structure of the *FLT3* protein presents all the characteristics of a receptor-type kinase of this family. The gene is expressed in placenta, in various adult tissues including gonads and brain, and in hematopoietic cells. The *Flt3* transcript is 3.7 kb long, except in the testis, where two shorter post-meiotic transcripts are detected. These results suggest a role for this novel receptor and its yet unidentified *ligand* in placenta, gonads and hematopoietic and nervous

systems.

3/3,AB/15 (Item 1 from file: 434)
DIALOG(R)File 434:SciSearch(R)

13601521 Genuine Article#: QA980 Number of References: 32 Title: IDENTIFICATION OF SOLUBLE AND MEMBRANE-BOUND ISOFORMS OF THE MURINE *FLT3* *LIGAND* GENERATED BY ALTERNATIVE SPLICING OF MESSENGER-RNAS Author(s): LYMAN SD; JAMES L; ESCOBAR S; DOWNEY H; DEVRIES P; BRASEL K; STOCKING K; BECKMANN MP; COPELAND NG; CLEVELAND LS; JENKINS NA; BELMONT JW; DAVISON BL
Corporate Source: IMMUNEX RES & DEV CORP,51 UNIV ST/SEATTLE//WA/98101; NCI,FREDERICK CANC RES & DEV CTR,ABL BASIC RES PROGRAM,MAMMALIAN GENET LAB/FREDERICK//MD/21702; BAYLOR COLL MED,INST MOLEC GENET/HOUSTON//TX/77030
Journal: ONCOGENE, 1995, V10, N1 (JAN 5), P149-157
ISSN: 0950-9232
Language: ENGLISH Document Type: ARTICLE
Abstract: We have recently described a novel hematopoietic growth factor, referred to as the *flt3* *ligand*, that stimulates the proliferation of sub-populations of hematopoietic cells that are enriched for stem and progenitor cells, This factor is a transmembrane protein that undergoes proteolytic cleavage to generate a soluble form of the protein. We have isolated additional *flt3* *ligand* isoforms by PCR that contain an extra exon and encode what are predicted to be either a soluble form of the *ligand* or a longer version of the transmembrane protein. We have also isolated cDNAs from murine T cell libraries that encode an isoform of the *flt3* *ligand* that has an unusual C-terminus, This isoform results from a failure to splice out an intron during mRNA processing. The protein encoded by this cDNA is expressed on the cell surface, where it is biologically active. However, this novel isoform does not appear to give rise to a soluble form of the protein, Regulation of mRNA splicing is likely to control the generation of cell bound or soluble forms of this hematopoietic growth factor, Genetic mapping studies localize the gene encoding the *flt3* *ligand* to the proximal portion of mouse chromosome 7 and to human chromosome 19q13.3.

3/3,AB/16 (Item 2 from file: 434)
DIALOG(R)File 434:SciSearch(R)

13562885 Genuine Article#: PY200 Number of References: 105 Title: TNF-ALPHA, THE GREAT IMITATOR - ROLE OF P55 AND P75 TNF RECEPTORS IN HEMATOPOIESIS
Author(s): JACOBSEN SEW; JACOBSEN FW; FAHLMAN C; RUSTEN LS Corporate Source: NORWEGIAN RADIUM HOSP,INST CANC RES,DEPT IMMUNOL/N-0310 OSLO//NORWAY/; HIPPLE CANC RES CTR/DAYTON//OH/45439
Journal: STEM CELLS, 1994, V12, S1, P111-128
ISSN: 1066-5099
Language: ENGLISH Document Type: REVIEW
Abstract: The clinical application of tumor necrosis factor-alpha (TNB-alpha) has so far been limited due to the severe adverse effects associated with its systemic use. Recently, two distinct TNF receptors with molecular weights of 55 kDa (TNFR55) and 75 kDa (TNFR75) have been cloned and characterized. The subsequent development of TNF-alpha r mutants with selective activity on either TNFR55 or TNFR75 suggest that such mutants might maintain the therapeutic (anti-tumor)

potential of wild type TNF-alpha, but exhibit reduced toxicity (proinflammatory effects). In the present article we discuss previous studies on the effects of TNF-alpha in in vitro and in vivo hematopoiesis. In addition, we summarize more recent data from our laboratory as well as others, elucidating the role of TNF-alpha as a direct bifunctional regulator of in vitro hematopoiesis. Specifically, TNF-alpha is a potent inhibitor of the clonal growth of primitive and committed murine and human bone marrow progenitors in combination with multiple cytokines, including granulocyte colony-stimulating factor (G-CSF), CSF-1, erythropoietin (Epo), stem cell factor (SCF), and *flt3* *ligand* (FL). In contrast, TNF-alpha at low concentrations can synergistically and directly enhance the clonal growth of primitive and more mature human CD34(+) bone marrow progenitors when combined with GM-CSF or interleukin (IL)-3. Thus, a critical determinant of whether TNF-alpha elicits a stimulatory or inhibitory effect on the in vitro growth of hematopoietic progenitors appears to be the specific growth factors with which it interacts, rather than the maturity of the targeted progenitor.

Furthermore, we describe the involvement of the two TNF receptors in signaling in vitro hematopoietic effects of TNF-alpha. Whereas TNFR55 is involved in most observed responses to TNF-alpha signaling of TNFR75 appears to be restricted to inhibitory effects on primitive progenitors. Finally, we discuss the complexity of direct and indirect actions of TNF-alpha in in vivo hematopoiesis, and the potential clinical applications of TNF-alpha or TNF mutants.

3/3,AB/17 (Item 3 from file: 434)
DIALOG(R)File 434:SciSearch(R)

13562884 Genuine Article#: PY200 Number of References: 28 Title: THE *FLT3* *LIGAND* - A HEMATOPOIETIC STEM-CELL FACTOR WHOSE ACTIVITIES ARE DISTINCT FROM STEEL FACTOR
Author(s): LYMAN SD; BRASEL K; ROUSSEAU AM; WILLIAMS DE
Corporate Source: IMMUNEX RES & DEV CORP,DEPT MOLEC GENET,51 UNIVST/SEATTLE//WA/98101
Journal: STEM CELLS, 1994, V12, S1, P99-110
ISSN: 1066-5099
Language: ENGLISH Document Type: ARTICLE
Abstract: A number of growth factors have been described that affect the hematopoietic system. Among this group are Steel factor (also known as mast cell growth factor, stem cell factor and kit *ligand*), and the more recently described *flt3* *ligand*. These factors have been shown to function by binding to and activating the c-kit and *flt3* tyrosine kinase receptors, respectively. Both of these factors stimulate the growth of mouse and human hematopoietic progenitor cells. These factors therefore differ from such later acting hematopoietic factors as colony-stimulating factor (CSF)-1, which regulates the growth, survival and differentiation of monocytic cells through the c-fms tyrosine kinase receptor. Like Steel factor, the *flt3* *ligand* has little biological activity on its own, but synergizes well with a number of other colony stimulating factors and interleukins. One major difference between the two factors appears to be their effect on mast cells. Steel factor stimulates both the proliferation and activation of mast cells, while preliminary data with the *flt3* *ligand* suggests that it has no effect on mast cells. Although the *flt3* *ligand* and Steel factor each act on early hematopoietic cells, differences in their activities suggest that they are not redundant and are both required for normal hematopoiesis.

3/3,AB/18 (Item 4 from file: 434)
DIALOG(R)File 434:SciSearch(R)

13503176 Genuine Article#: PR754 Number of References: 0 Title: *FLT3* *LIGAND* (FL) SUPPORTS PROLIFERATION OF LYMPHOHEMATOPOIETIC AND EARLY B-LYMPHOID PROGENITORS
Author(s): HIRAYAMA F; LYMAN SD; CLARK SC; OGAWA M
Corporate Source: MED UNIV S CAROLINA,DEPT MED/CHARLESTON//SC/29425; VET ADM MED CTR/CHARLESTON//SC/29403; IMMUNEX CORP/SEATTLE//WA/00000 Journal: BLOOD, 1994, V84, N10 (NOV 15), PA512
ISSN: 0006-4971
Language: ENGLISH Document Type: MEETING ABSTRACT

3/3,AB/19 (Item 5 from file: 434)
DIALOG(R)File 434:SciSearch(R)

13502601 Genuine Article#: PR754 Number of References: 0 Title: *FLT3* *LIGAND* (FLT3L) AND STEM-CELL FACTOR (SCF) SUPPORT THE EX-VIVO EXPANSION OF PRIMITIVE HUMAN HEMATOPOIETIC-CELLS - RESPONSE OF LONG-TERM CULTURE INITIATING CELLS (LTCIC) AND CD34+ CD38DIM CELLS Author(s): DOOLEY DC; HEINRICH M; PLUNKETT JM; OPPENLANDER BK; PEETOOM F Corporate Source: AMER RED CROSS,PACIFIC NW REG BLOOD SERV/PORTLAND//OR/00000; VET ADM MED CTR/PORTLAND//OR/97207 Journal: BLOOD, 1994, V84, N10 (NOV 15), PA368
ISSN: 0006-4971
Language: ENGLISH Document Type: MEETING ABSTRACT

3/3,AB/20 (Item 6 from file: 434)
DIALOG(R)File 434:SciSearch(R)

13502244 Genuine Article#: PR754 Number of References: 0 Title: THE ROLE OF *FLT3* *LIGAND* IN EARLY MURINE HEMATOPOIESIS Author(s): DEVRIES P; BRASEL KA; MCKENNA HJ; WILLIAMS DE; LYMAN SD Corporate Source: IMMUNEX CORP/SEATTLE//WA/00000
Journal: BLOOD, 1994, V84, N10 (NOV 15), PA279
ISSN: 0006-4971
Language: ENGLISH Document Type: MEETING ABSTRACT

3/3,AB/21 (Item 7 from file: 434)
DIALOG(R)File 434:SciSearch(R)

13502205 Genuine Article#: PR754 Number of References: 0 Title: MODULATION OF HEMATOPOIETIC PROGENITOR DEVELOPMENT BY RECOMBINANT HUMAN *FLT3* *LIGAND* Author(s): BANU N; DENG B; LYMAN S; GROOPMAN JE; AVRAHAM H Corporate Source: HARVARD UNIV,SCH MED,DEACONESS HOSP,DIV

HEMATOLONCOL/BOSTON//MA/02115; IMMUNEX CO/SEATTLE//WA/00000 Journal: BLOOD, 1994, V84, N10 (NOV 15), PA269
ISSN: 0006-4971
Language: ENGLISH Document Type: MEETING ABSTRACT

3/3,AB/22 (Item 8 from file: 434)
DIALOG(R)File 434:SciSearch(R)

13502013 Genuine Article#: PR754 Number of References: 0 Title: AUTOCRINE INHIBITION BY TGF-BETA-1 SUPPRESSES *FLT3* *LIGAND* (FLT3L) AND STEM-CELL FACTOR (SCF) STIMULATED GROWTH - EVIDENCE FOR TGF-BETA-1 GENE-EXPRESSION IN HEMATOPOIETIC-CELLS
Author(s): ZHU XL; NOVAK FP; HEINRICH M; OPPENLANDER BK; DOOLEY DC Corporate Source: AMER RED CROSS,PACIFIC NW REG BLOOD SERV/PORTLAND//OR/00000; VET ADM MED CTR/PORTLAND//OR/97207 Journal: BLOOD, 1994, V84, N10 (NOV 15), PA221
ISSN: 0006-4971
Language: ENGLISH Document Type: MEETING ABSTRACT

3/3,AB/23 (Item 9 from file: 434)
DIALOG(R)File 434:SciSearch(R)

13501640 Genuine Article#: PR754 Number of References: 0 Title: THE STIMULATORY COSTIMULATORY EFFECTS OF *FLT3*-*LIGAND* ON HUMAN MYELOID-LEUKEMIA CELLS
Author(s): PIACIBELLO W; FUBINI L; SEVERINO A; SANAVIO F; GARETTO L; STACCHINI A; LYMAN S; AGLIETTA M
Corporate Source: UNIV TURIN,DEPT BIOMED SCI & HUMAN ONCOL/I-10124 TURIN//ITALY/; IMMUNEX CORP/SEATTLE//WA/00000
Journal: BLOOD, 1994, V84, N10 (NOV 15), PA127
ISSN: 0006-4971
Language: ENGLISH Document Type: MEETING ABSTRACT

3/3,AB/24 (Item 10 from file: 434)
DIALOG(R)File 434:SciSearch(R)

13501639 Genuine Article#: PR754 Number of References: 0 Title: EXPRESSION OF *FLT3* AND *FLT3*-*LIGAND* IN A PANEL OF HUMAN LEUKEMIA-LYMPHOMA CELL-LINES
Author(s): MEIERHOFF G; DIRKS W; GRUSS HJ; HU ZB; ROSNET O; BIRNBAUM D; DREXLER HG
Corporate Source: DSM,DEPT HUMAN & ANIM CELL CULTURES,GERMAN COLLECT MICROORGANISMS & CELL CULTURE/BRAUNSCHWEIG//GERMANY/; IMMUNEX RES & DEV CORP/SEATTLE//WA/00000; INSERM,U119/F-13258 MARSEILLE 09//FRANCE/ Journal: BLOOD, 1994, V84, N10 (NOV 15), PA127
ISSN: 0006-4971

Language: ENGLISH Document Type: MEETING ABSTRACT

3/3,AB/25 (Item 11 from file: 434)
DIALOG(R)File 434:SciSearch(R)

13501341 Genuine Article#: PR754 Number of References: 0 Title: THE EFFECT OF *FLT3* *LIGAND* ON PRIMARY ACUTE HUMAN LEUKEMIAS Author(s): MCKENNA HJ; SMITH FO; DEVRIES P; BRASEL K; LYMAN SD; WILLIAMS DE Corporate Source: INDIANA UNIV,SCH MED/INDIANAPOLIS//IN/46202; CHILDRENS CANC GRP/ARCADIA//CA/00000; IMMUNEX CORP/SEATTLE//WA/00000 Journal: BLOOD, 1994, V84, N10 (NOV 15), PA52
ISSN: 0006-4971
Language: ENGLISH Document Type: MEETING ABSTRACT

3/3,AB/26 (Item 12 from file: 434)
DIALOG(R)File 434:SciSearch(R)

13261352 Genuine Article#: PB368 Number of References: 0 Title: THE BIOLOGICAL EFFECTS OF *FLT3* *LIGAND* ON CD34 POSITIVE PROGENITOR CELLS ISOLATED FROM HUMAN BONE-MARROW AND CORD-BLOOD Author(s): MCKENNA HJ; LYMAN SD; DEVRIES P; BRASEL KA; BECKMANN MP; WILLIAMS DE
Corporate Source: IMMUNEX CORP/SEATTLE//WA/00000
Journal: EXPERIMENTAL HEMATOLOGY, 1994, V22, N8 (AUG), P763 ISSN: 0301-472X
Language: ENGLISH Document Type: MEETING ABSTRACT

3/3,AB/27 (Item 13 from file: 434)
DIALOG(R)File 434:SciSearch(R)

13261316 Genuine Article#: PB368 Number of References: 0 Title: ALTERNATIVE SPLICING OF MURINE AND HUMAN *FLT3* *LIGAND* MESSENGER-RNAS REGULATES PRODUCTION OF CELL-BOUND AND SOLUBLE FORMS OF THE PROTEIN
Author(s): LYMAN SD; JAMES L; ESCOBAR SS; BRASEL K; DOWNEY H; STOCKING K; DAVISON B; BECKMANN MP; DEVRIES P
Corporate Source: IMMUNEX RES & DEV CORP/SEATTLE//WA/98101 Journal: EXPERIMENTAL HEMATOLOGY, 1994, V22, N8 (AUG), P753 ISSN: 0301-472X
Language: ENGLISH Document Type: MEETING ABSTRACT

3/3,AB/28 (Item 14 from file: 434)
DIALOG(R)File 434:SciSearch(R)

13261253 Genuine Article#: PB368 Number of References: 0 Title: *FLT3*/*FLK2*-*LIGAND* STIMULATES THE GROWTH OF HUMAN FETAL LIVER PROGENITORS
Author(s): MUENCH MO; MENON S; KASTELEIN R; HANNUM C; CULPEPPER J; ZURAWSKI S;

CUPP J; LEE F; RONCAROLO MG; NAMIKAWA R
Corporate Source: DNAX RES INST MOLEC & CELLULAR BIOL INC/PALO ALTO//CA/94304
Journal: EXPERIMENTAL HEMATOLOGY, 1994, V22, N8 (AUG), P737 ISSN: 0301-472X
Language: ENGLISH Document Type: MEETING ABSTRACT

3/3,AB/29 (Item 15 from file: 434)
DIALOG(R)File 434:SciSearch(R)

13261251 Genuine Article#: PB368 Number of References: 0 Title: RECOMBINANT *FLT3* *LIGAND* ENHANCES HEMATOPOIESIS IN MYELOID AND B-LYMPHOID LONG-TERM BONE-MARROW CULTURES
Author(s): BRASEL K; ROUSSEAU AM; DEVRIES P; LYMAN SD; WILLIAMS DE Corporate Source: IMMUNEX RES & DEV CORP/SEATTLE//WA/98101 Journal: EXPERIMENTAL HEMATOLOGY, 1994, V22, N8 (AUG), P736 ISSN: 0301-472X
Language: ENGLISH Document Type: MEETING ABSTRACT

3/3,AB/30 (Item 16 from file: 434)
DIALOG(R)File 434:SciSearch(R)

13261211 Genuine Article#: PB368 Number of References: 0 Title: *FLT3* *LIGAND* STIMULATION OF DISTINCT HEMATOPOIETIC-CELL POPULATIONS ISOLATED FROM MURINE FETAL LIVER
Author(s): GLINIAK BC; FOXWORTHE D; DEVRIES P; BRASEL KA; HIRSCHSTEIN D; BECKMANN MP; WILLIAMS DE; LYMAN SD
Corporate Source: IMMUNEX RES & DEV CORP/SEATTLE//WA/98101 Journal: EXPERIMENTAL HEMATOLOGY, 1994, V22, N8 (AUG), P725 ISSN: 0301-472X
Language: ENGLISH Document Type: MEETING ABSTRACT

3/3,AB/31 (Item 17 from file: 434)
DIALOG(R)File 434:SciSearch(R)

13261210 Genuine Article#: PB368 Number of References: 0 Title: STIMULATING CO-STIMULATING EFFECTS OF *FLT* *3*-*LIGAND* ON IMMATURE SUBSETS OF MYELOID STEM/PROGENITOR CELLS
Author(s): BROXMEYER HE; LU L; COOPER S; LI ZH; MCKENNA HJ; WILLIAMS DE; BECKMANN MP; LYMAN SD
Corporate Source: INDIANA UNIV,SCH MED,WALTHER ONCOL CTR/INDIANAPOLIS//IN/46202; IMMUNEX CORP/SEATTLE//WA/00000 Journal: EXPERIMENTAL HEMATOLOGY, 1994, V22, N8 (AUG), P725 ISSN: 0301-472X
Language: ENGLISH Document Type: MEETING ABSTRACT

3/3,AB/32 (Item 18 from file: 434)
DIALOG(R)File 434:SciSearch(R)

13261206 Genuine Article#: PB368 Number of References: 0 Title: THE EFFECTS OF SOLUBLE *FLT3* *LIGAND* ON MURINE PLURIPOTENT HEMATOPOIETIC STEM-CELLS
Author(s): DEVRIES P; BRASEL KA; MCKENNA HJ; BECKMANN MP; GLINIAK BC; WILLIAMS DE; LYMAN SD; PATCHEN ML
Corporate Source: IMMUNEX CORP/SEATTLE//WA/00000
Journal: EXPERIMENTAL HEMATOLOGY, 1994, V22, N8 (AUG), P724 ISSN: 0301-472X
Language: ENGLISH Document Type: MEETING ABSTRACT

3/3,AB/33 (Item 19 from file: 434)
DIALOG(R)File 434:SciSearch(R)

13261193 Genuine Article#: PB368 Number of References: 0 Title: THE EFFECT OF *FLT3* *LIGAND* ON THE GROWTH OF MYELOID AND LYMPHOID PROGENITOR CELLS
Author(s): HUNTE B; HUDAK S; MENON S; HANNUM C; LEE F; CAMPBELL D; CULPEPPER J; RENNICK D
Corporate Source: DNAX RES INST MOLEC & CELLULAR BIOL INC/PALO ALTO//CA/94304
Journal: EXPERIMENTAL HEMATOLOGY, 1994, V22, N8 (AUG), P720 ISSN: 0301-472X
Language: ENGLISH Document Type: MEETING ABSTRACT

3/3,AB/34 (Item 20 from file: 434)
DIALOG(R)File 434:SciSearch(R)

13258812 Genuine Article#: PB581 Number of References: 27 Title: GENOMIC STRUCTURE OF THE DOWNSTREAM PART OF THE HUMAN *FLT3* GENE - EXON/INTRON STRUCTURE CONSERVATION AMONG GENES ENCODING RECEPTOR TYROSINE KINASES (RTK) OF SUBCLASS-III
Author(s): AGNES F; SHAMOON B; DINA C; ROSNET O; BIRNBAUM D; GALIBERT F Corporate Source: FAC MED RENNES,BIOCHIM & BIOL MOLEC LAB,CNRS,UPR 41,2 AVE PROFESSEUR LEON BERNARD/F-35043 RENNES//FRANCE/; INSERM,U119/F-13009 MARSEILLE//FRANCE/
Journal: GENE, 1994, V145, N2 (AUG 5), P283-288
ISSN: 0378-1119
Language: ENGLISH Document Type: NOTE
Abstract: The *FLT3* gene encodes a subclass-III receptor tyrosine kinase (RTKIII). We have determined the structural organization of the downstream part of the human *FLT3* gene (also designated dsp-*FLT3*) that corresponds to the intracellular region of the protein. The coding region is spread over twelve exons spanning 10 kb of genomic DNA. Exon sizes range from 83 to 154 bp, while intron sizes range from 86 bp to more than 1.9 kb. Comparison with the corresponding domain of other RTKIII genes (KIT and FMS) shows that these genes share the same number of exons, which are highly conserved in size, sequence and exon/intron boundary positions. In addition, the intron phase of equivalent introns of *FLT3*, KIT and FMS are all identical. Our results reinforce our hypothesis based initially only on the KIT and FMS comparison showing that RTKIII genes share a common structural organization and have evolved from a common ancestor gene by cis and tl ans duplication. Comparison of the genomic organization of the intracellular-encoding part of RTKIII genes with that of RTKI, II and IV genes shows that subclasses III and IV are the most closely related.

3/3,AB/35 (Item 21 from file: 434)
DIALOG(R)File 434:SciSearch(R)

13208731 Genuine Article#: NX139 Number of References: 28 Title: BIOLOGICAL PROPERTIES OF SUBPOPULATIONS OF PLURIPOTENT HEMATOPOIETIC STEM-CELLS ENRICHED BY ELUTRIATION AND FLOW-CYTOMETRY
Author(s): ORLIC D; ANDERSON S; BODINE DM
Corporate Source: NIH,NATL CTR HUMAN GENOME RES,HEMATOPOIESIS SECT,GENE TRANSFER LAB,9000 ROCKVILLE PK/BETHESDA//MD/20892; NHLBI,CLIN HEMATOL BRANCH/BETHESDA//MD/20892
Journal: BLOOD CELLS, 1994, V20, N1, P107-120
ISSN: 0340-4684
Language: ENGLISH Document Type: ARTICLE
Abstract: We have studied several features of pluripotent hematopoietic stem cells (PMSCs) and day-12 spleen colony-forming units (CFU-S) obtained from adult murine bone marrow. Single-cell suspensions of C57BL/6J mouse bone marrow were fractionated by counterflow centrifugal elutriation at flow rates (FR) of 15, 25, 30, and 35 ml/min, and with the rotor off (R/O), The fractions FR25 and FR35 contained approximately equal numbers of PHSC that could repopulate W/W-v mice. These PHSCs were further enriched by subtracting lineage-positive cells using monoclonal antibodies (MAb) and magnetic immunobeads. The resulting lineage-negative cells (Lin(-)) were then stained with a MAb for the c-kit receptor and sorted by flow cytometry. Both subsets were fractionated into cells expressing high (bright) (c-kit(BR)), low (dull) c-kit(DULL) and (negative, c-kit(NEG)) c-kit receptor. As few as 100 to 200 c-kit(BR) cells could repopulate the entire thymus and bone marrow in W/W-v mice. No PHSCs were present in the c-kit(DULL) and c-kit(NEG) fractions. We assayed fresh bone marrow and elutriation fractions FR25 and FR35 for gene expression by reverse transcriptase polymerase chain reaction. Using a semiquantitative protocol, we detected mRNA for beta-globin and *flk*-*2*, a protein tyrosine kinase receptor, in all samples except the FR25 Lin(-) c-kit(BR) subset. We consider the cells in FR25 Lin(-) c-kit(BR) to be the most primitive set of hematopoietic stem cells.

3/3,AB/36 (Item 22 from file: 434)
DIALOG(R)File 434:SciSearch(R)

13133025 Genuine Article#: NQ977 Number of References: 23 Title: DEVELOPMENTAL EXPRESSION OF *FLT3* MESSENGER-RNA IN THE MOUSE-BRAIN
Author(s): ITO A; HIROTA S; KITAMURA Y; NOMURA S
Corporate Source: OSAKA UNIV,SCH MED,DEPT PATHOL,2-2 YAMADAOKA/SUITA/OSAKA 565/JAPAN/; OSAKA UNIV,SCH MED,DEPT PATHOL,2-2 YAMADAOKA/SUITA/OSAKA 565/JAPAN/
Journal: JOURNAL OF MOLECULAR NEUROSCIENCE, 1993, V4, N4 (WIN), P235-243 ISSN: 0895-8696
Language: ENGLISH Document Type: ARTICLE
Abstract: The expression and localization of *flt3* mRNA were investigated using Northern blotting and in situ hybridization during the developmental process of the mouse brain. By Northern blotting, the expression of the *flt3* gene was not detected in embryonic, neonatal, or early postnatal brains, but was markedly increased with age. In adult mice,*flt3* was abundantly expressed in the cerebellum, moderately in the pons, and faintly in the thalamus and the cerebral cortex. By in situ

hybridization, some neurons that expressed *flt3* formed synaptic connections with each other. The present findings suggest that the *flt3* gene expression is related to the cell type and the developmental process.

3/3,AB/37 (Item 23 from file: 434)
DIALOG(R)File 434:SciSearch(R)

13104255 Genuine Article#: NP119 Number of References: 19 Title: EXPRESSION OF THE *FLT3* GENE IN HUMAN LEUKEMIA-LYMPHOMA CELL-LINES Author(s): DASILVA N; HU ZB; MA WL; ROSNET O; BIRNBAUM D; DREXLER HG Corporate Source: DSM,GERMAN COLLECT MICROORGANISMS & CELL CULTURES,DEPT HUMAN & ANIM CELL CULTURES/D-38124 BRAUNSCHWEIG//GERMANY/; DSM,GERMAN COLLECT MICROORGANISMS & CELL CULTURES,DEPT HUMAN & ANIM CELL CULTURES/D-38124 BRAUNSCHWEIG//GERMANY/; INSERM,U119/MARSEILLE//FRANCE/ Journal: LEUKEMIA, 1994, V8, N5 (MAY), P885-888
ISSN: 0887-6924
Language: ENGLISH Document Type: NOTE
Abstract: The *FLT3* gene encodes a protein that appears to function as a receptor for a hematopoietic growth factor; together with the KIT and FMS receptors, *FLT3* belongs to the superfamily of receptors with tyrosine kinase activity. We examined the expression of *FLT3* mRNA in 36 human leukemia-lymphoma cell lines using Northern blot analysis. *FLT3* transcripts were found in seven of seven pre B-ALL cell lines (derived from cases with pre B-acute lymphoblastic leukemia or chronic myeloid leukemia in lymphoid blast crisis), and in one of six B-cell lines (namely in a cell line established from a hairy cell leukemia). *FLT3* message was not detected in five T-cell, five myeloid, four monocytic, four erythroid and five megakaryocytic cell lines. Two major mRNA species were expressed differentially by positive cell lines. KIT mRNA expression was also investigated in the same panel of cell lines, but was found only in cell lines with erythroid and megakaryocytic features (and not in any of the *FLT3*-positive cell lines). The pattern of expression of *FLT3* contrasts with the transcription of FMS and KIT and suggests that the *FLT3* product may play a role primarily in immature lymphoid cells.

3/3,AB/38 (Item 24 from file: 434)
DIALOG(R)File 434:SciSearch(R)

12944842 Genuine Article#: ND197 Number of References: 0 Title: CHARACTERIZATION OF THE *LIGAND* FOR *FLT3*/*FLK2*
Author(s): CULPEPPER J; HANNUM C; MATTSON J; LUH J; MCCLANAHAN T; CAMPBELL D; ZURAWSKI S; WAGNER J; HUDAK S; MARTINA N; RENNICK D; PETERSON D; KASTELEIN R; MENON S; DANG W; BAZAN JF; MUENCH M; KELNER G; RONCAROLO MG; ZLOTNIK A; ROSNET O; DUBREUIL P; BIRNBAUM D; LEE F Corporate Source: DNAX RES INST MOLEC & CELLULAR BIOL INC,RES INST/PALO ALTO//CA/94304; INSERM,U119/F-13009 MARSEILLE//FRANCE/ Journal: FASEB JOURNAL, 1994, V8, N5 (MAR 18), PA963
ISSN: 0892-6638
Language: ENGLISH Document Type: MEETING ABSTRACT

3/3,AB/39 (Item 25 from file: 434)

DIALOG(R)File 434:SciSearch(R)

12850063 Genuine Article#: MV412 Number of References: 0 Title: THE *LIGAND* FOR *FLT3*/*FLK2*
Author(s): HANNUM C; CULPEPPER J; CAMPBELL D; MCCLANAHAN T; DUDA G; ZURAWSKI S; RENNICK D; WAGNER J; MARTINA N; KASTELEIN R; SHANAFELT A; PETERSON D; MENON S; DANG W; MATTSON J; LUH J; BAZAN F; ROSNET O; DUBREUIL P; BIRNBAUM D; LEE F
Corporate Source: DNAX RES INST MOLEC & CELLULAR BIOL INC,RES INST/PALO ALTO//CA/94304; INSERM/F-13009 MARSEILLE//FRANCE/
Journal: JOURNAL OF CELLULAR BIOCHEMISTRY, 1994, S18A (JAN 4), P19 ISSN: 0730-2312
Language: ENGLISH Document Type: MEETING ABSTRACT

3/3,AB/40 (Item 26 from file: 434)
DIALOG(R)File 434:SciSearch(R)

12850041 Genuine Article#: MV412 Number of References: 0 Title: MOLECULAR-CLONING OF A *LIGAND* FOR THE *FLT3*/*FLK*-*2* TYROSINE KINASE RECEPTOR THAT IS BIOLOGICALLY-ACTIVE ON PRIMITIVE HEMATOPOIETIC-CELLS
Author(s): LYMAN SD; JAMES L; VANDENBOS T; BRASEL K; DEVRIES P; PICHA KS; FARRAH T; HOLLINGSWORTH T; GLINIAK B; MCKENNA HJ; FLETCHER FA; SPLETT R ; MARASKOVSKY E; WILLIAMS DE; BECKMANN MP
Corporate Source: IMMUNEX RES & DEV CORP/SEATTLE//WA/98101 Journal: JOURNAL OF CELLULAR BIOCHEMISTRY, 1994, S18A (JAN 4), P13 ISSN: 0730-2312
Language: ENGLISH Document Type: MEETING ABSTRACT

3/3,AB/41 (Item 27 from file: 434)
DIALOG(R)File 434:SciSearch(R)

12802415 Genuine Article#: MR989 Number of References: 39 Title: STK-1, THE HUMAN HOMOLOG OF *FLK*-*2*/*FLT*-*3*, IS SELECTIVELY EXPRESSED IN CD34(+) HUMAN BONE-MARROW CELLS AND IS INVOLVED IN THE PROLIFERATION OF EARLY PROGENITOR STEM-CELLS
Author(s): SMALL D; LEVENSTEIN M; KIM E; CAROW C; AMIN S; ROCKWELL P; WITTE L; BURROW C; RATAJCZAK MZ; GEWIRTZ AM; CIVIN CI
Corporate Source: JOHNS HOPKINS UNIV,SCH MED,CTR ONCOL,600 N WOLFE ST/BALTIMORE//MD/21287; JOHNS HOPKINS UNIV,SCH MED,DEPT PEDIAT/BALTIMORE//MD/21287; JOHNS HOPKINS UNIV,SCH MED,DEPT NEPHROL/BALTIMORE//MD/21287; UNIV PENN,SCH MED,DEPT LAB MED/PHILADELPHIA//PA/19104; UNIV PENN,SCH MED,DEPT PATHOL/PHILADELPHIA//PA/19104; UNIV PENN,SCH MED,DEPT MED/PHILADELPHIA//PA/19104; IMCLONE SYST INC/NEW YORK//NY/10014 Journal: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, 1994, V91, N2 (JAN 18), P459-463
ISSN: 0027-8424
Language: ENGLISH Document Type: ARTICLE

Abstract: We cloned the cDNA for stem cell tyrosine kinase 1 (STR-1), the human homolog of murine *Flk*-*2*/*Flt*-*3*, from a CD34(+) hematopoietic stem cell-enriched library and investigated its expression in subsets of normal human bone marrow. The cDNA encodes a protein of 993 aa with 85% identity and 92% similarity to *FLk*-*2*/ *Flt*-*3*. STK-1 is a member of the type m receptor tyrosine kinase family that includes KIT (steel factor receptor), FMS (colony-stimulating factor 1R), and platelet derived growth factor receptor. STK-1 expression in human blood and marrow is restricted to CD34(+) cells, a population greatly enriched for stem/progenitor cells. Anti-STK-1 antiserum recognizes polypeptides of 160 and 130 kDa in several STK-1 expressing cell lines and in 3T3 cells transfected with a STK-1 expression vector. Antisense oligonucleotides directed against STK-1 sequences inhibited hematopoietic colony formation, most strongly in long-term bone marrow cultures. These data suggest that STK-1 may function as a growth factor receptor on hematopoietic stem and/or progenitor cells.

3/3,AB/42 (Item 28 from file: 434)
DIALOG(R)File 434:SciSearch(R)

12686592 Genuine Article#: MF563 Number of References: 189 Title: HEMATOPOIETIC RECEPTORS OF CLASS-III RECEPTOR-TYPE TYROSINE KINASES Author(s): ROSNET O; BIRNBAUM D
Corporate Source: INSERM,U119,ONCOL MOLEC LAB,27 BD LEI ROURE/F-13258 MARSEILLE 09//FRANCE/; INSERM,U119,ONCOL MOLEC LAB,27 BD LEI ROURE/F-13258 MARSEILLE 09//FRANCE/
Journal: CRITICAL REVIEWS IN ONCOGENESIS, 1993, V4, N6, P595-613 ISSN: 0893-9675
Language: ENGLISH Document Type: REVIEW
Abstract: Receptor-type tyrosine kinases (RTKs) constitute a family of proteins involved in growth and developmental processes. Class III RTKs are characterized by an extracellular region composed of five immunoglobulin-like domains and by a split tyrosine kinase domain. Some of the class III RTKs perform major functions in hematopoiesis and are the focus of this review. They are the colony-stimulating factor-1 (CSF1) and Steel factor (SLF) receptors, encoded by the FMS and KIT protooncogenes, respectively, and the product of the *FLT3*/*FLK2* gene. The structural, biochemical, functional, and pathological features of these three receptors and genes are reviewed.

3/3,AB/43 (Item 29 from file: 434)
DIALOG(R)File 434:SciSearch(R)

12477298 Genuine Article#: LP542 Number of References: 29 Title: THE EXPRESSION OF CYTOKINE RECEPTORS BY PURIFIED HEMATOPOIETIC STEM-CELLS
Author(s): VISSER JWM; ROZEMULLER H; DEJONG MO; BELYAVSKY A Corporate Source: TNO,INST MED BIOL,DEPT MOLEC PATHOL,POB 5815/2280 HV RIJSWIJK//NETHERLANDS/; TNO,INST APPL RADIOBIOL & IMMUNOL/RIJSWIJK//NETHERLANDS/; WA ENGELHARDT MOLEC BIOL INST/MOSCOW//RUSSIA/
Journal: STEM CELLS, 1993, V11, S2 (JUL), P49-55
ISSN: 1066-5099
Language: ENGLISH Document Type: ARTICLE
Abstract: Sorted fractions from mouse bone marrow containing highly purified hemopoietic stem and progenitor cells were studied for the expression of growth factor receptors. With the use of

rhodamine 123 WGA+, 15-1.1-, low density cells were separated into quiescent pluripotent stem cells and committed progenitor cells. RNA was extracted and cDNA was prepared by reverse transcription. Using primers specific for growth factor receptors, the cDNA of each sorted fraction was amplified by polymerase chain reaction (PCR).

The quiescent rhodamine 123 dull stem cell fraction was found to express the interleukin 3 (IL-3) receptor beta unit and c-kit, but not the granulocyte-macrophage colony stimulating factor (GM-CSF) receptor beta unit nor *flk*-*2*. The rhodamine 123 bright fraction with activated stem cells and mostly committed progenitor cells similarly expressed the IL-3-Rbeta, and c-kit. However, this fraction also expressed *flk*-*2* and GM-CSF-Rbeta.

Since the expression of c-kit in the stem cell fraction does not correspond with the poor response to the kit-*ligand* stem cell factor (SCF) by these cells, we further analyzed the fractions with respect to their binding of biotinylated SCF. The SCF-binding cells were found to be all rhodamine 123 bright. This indicates that the expression of c-kit is not sufficient to yield a functional receptor for SCF; c-kit probably needs a partner molecule to form a functional high-affinity binding site for SCF. Similar to the beta unit of the GM-CSF receptor, this partner is then not expressed in the stem cell fraction. Its expression would be upregulated upon differentiation and commitment. It may be speculated that this partner molecule of c-kit is *flk*-*2*. Alternatively, it may be speculated that the stem cells contain an isoform splice product of kit that has a reduced capability for dimerization.

3/3,AB/44 (Item 1 from file: 351)
DIALOG(R)File 351:DERWENT WPI

010150762 WPI Acc No: 95-052014/07
XRAM Acc No: C95-023855
Ligand for receptor protein tyrosine kinase - useful for the stimulation of primitive haematopoietic stem cells causing proliferation and/or differentiation
Patent Assignee: (UYPR-) UNIV PRINCETON
Author (Inventor): LEMISCHKA I R
Patent Family:
CC Number Kind Date Week
WO 9500554 A2 950105 9507 (Basic)
Priority Data (CC No Date): US 80244 (930618); US 81508 (930621); US 157490 (931123)
Applications (CC,No,Date): WO 94US6944 (940617)
Abstract (Basic): WO 9500554 A
A protein (A) binding to the receptor protein tyrosine kinase, *Flk2*, comprises the sequence AQSLSFXFTKFDLD, where X is any amino acid.
USE - (A) is a *ligand* for the receptor protein tyrosine kinase and can be used to stimulate the proliferation and/or differentiation of primitive haematopoietic stem cells. (A) binds to a receptor protein tyrosine kinase expressed in primitive but not mature mammalian haematopoietic cells.
Dwg.0/4

3/3,AB/45 (Item 2 from file: 351)
DIALOG(R)File 351:DERWENT WPI

010106818 WPI Acc No: 95-008071/02
XRAM Acc No: C95-002982
Isolated ligands for *flt* *3* receptors - useful for treating anaemia, AIDS and various cancers
Patent Assignee: (IMMV) IMMUNEX CORP
Author (Inventor): BECKMANN M P; LYMAN S D
Patent Family:

CC Number	Kind	Date	Week	
EP 627487	A2	941207	9502	(Basic)
WO 9428391	A1	941208	9503	
AU 9469877	A	941220	9512	

Priority Data (CC No Date): US 68394 (930524); US 106463 (930812); US 111758 (930825); US 162407 (931203); US 209502 (940307); US 243545 (940511)
Applications (CC,No,Date): AU 9469877 (940512); WO 94US5365 (940512); EP 94303575 (940519); WO 94US5365 (940512)
Abstract (Basic): EP 627487 A

An isolated *flt* *3*-*ligand* (*flt* *3*-L) polypeptide (I) is new. Also claimed are (1) a DNA sequence encoding (I), (2) an expression vector encoding the comprising the DNA of (1), (3) a host cell transfected with the expression vector of (2), (4) production of the *flt3*-L by culture of the host cell of (3) and retrieval of *flt3* -L from the culture supernatant, (5) an antibody that is immunoreactive with (I), (6) a haematopoietic cell expansion media comprising cell growth media and a *flt3*-L polypeptide, (7) a method of transfecting an exogenous gene into an early haematopoietic cell comprising (a) culturing the cells in media comprising an effective amount of *flt3*-L polypeptide; and (b) transfecting the cultured cells from step (a) with the gene, (8) a transgenic non-human animal all of whose germ cells and somatic cells at an embryonic stage contain the DNA of (1) or an ancestor of the transgenic animal; and (9) a method of sepg. cells with surface *flt* *3* receptors from a mixt. of cells in suspension by contacting the cells in the mixt. with a contacting surface having a *flt3*-binding protein (pref. (I), and sepg. the contacting surface and the suspension.

USE - (I) can be used in gene therapy and in the treatment of myelodysplastic syndrome, a plastic anaemia, HIV infection (AIDS), and cancers, such as breast cancer, lymphoma, acute leukaemia, testicular tumours and ovarian cancer. Other applicns. of (I) include to expand progenitor or stem cells collected from umbilical cord blood, and to stimulate prodn. of erythroid cells in vivo for treatment of anaemia esp. in AIDS patients receiving AZT therapy. The above treatments are pref. in conjunction with cytokines. A progenitor or stem cell expansion media is provided comprising (I) opt. in combination with a cytokine growth factor selected from CSF-1, GM-CSF, SF, G-CSF, EPO, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, GM-CSF/IL-3 fusion proteins, LIF and FGF and sequential or concurrent combinations of these.

Dwg.0/0

3/3,AB/46 (Item 3 from file: 351)
DIALOG(R)File 351:DERWENT WPI

010105534 WPI Acc No: 95-006787/01
XRAM Acc No: C95-002440
XRPX Acc No: N95-005473
New *ligand* for the *Flt3* tyrosine kinase receptor - and related nucleic acid, vectors, host cells and antibodies, useful for treating abnormal cell physiology and proliferation, e.g. cancer, also for

diagnosis and drug screening
Patent Assignee: (INRM) INST NAT SANTE & RECH MEDICALE; (SCHE) SCHERING CORP
Author (Inventor): BIRNBAUM D; CULPEPPER J A; HANNUM C H; LEE F D Patent Family:
CC Number Kind Date Week
WO 9426891 A2 941124 9501 (Basic)
Priority Data (CC No Date): US 65231 (930519); US 89263 (930707); US 92549 (930716); US 106340 (930813); US 112391 (930824); US 155111 (931119); US 162413 (931203)
Applications (CC,No,Date): WO 94US5150 (940518)
Abstract (Basic): WO 9426891 A

Pure mammalian *Flt3* (a tyrosine kinase receptor) *ligand* (I), or fragments of it, are new. Also new are (1) isolated nucleic acid (II) encoding (I); (2) recombinant vectors contg. (II); (3) host cells contg. such vectors; (4) antibodies (Ab), and their binding fragments, that bind specifically to (I). The specification includes sequences of 5 (human or murine) variants of (I), with 219-245 amino acids, also of DNA encoding (I).

USE - (I) is involved in regulation of physiology and development in many cell lineages, e.g. it interacts synergistically with cytokines to promote growth of stem cells, myeloid precursors, thymocytes etc. (I), its fragments and Ab may be used therapeutically to treat conditions of abnormal proliferation or degeneracy (e.g. cancer), partic. to modulate development of lymphoid cells which affect the immune response (autoimmune disease). (I) can also be used to measure binding affinity of test cpds. (potential agonists or antagonists for modulating physiology and development of haematopoietic and other cells); to generate Ab and to inhibit (I) function (when used as soluble fragments). Ab is used to assay (I) for diagnostic purposes (overexpression of (I) may indicate cancer or other abnormal cell proliferation), to block (I) function (if neutralising); when coupled to a radioisotope, toxin or drug, for targeted killing or treatment of cells, and for (I) purifcn. Fragments of (II) are useful as probes for detecting (I)-related nucleic acid sequences.

Dwg.0/0

3/3,AB/47 (Item 4 from file: 351)
DIALOG(R)File 351:DERWENT WPI

009755228 WPI Acc No: 94-035079/04
XRAM Acc No: C94-016251
New soluble and human foetal liver kinase-2 DNA sequences - used for obtaining prods. for modulating the growth of haematopoietic progenitor cells
Patent Assignee: (SYST-) SYSTEMIX INC
Author (Inventor): YANG Z
Patent Family:
CC Number Kind Date Week
WO 9401576 A1 940120 9404 (Basic)
AU 9346675 A 940131 9422
Priority Data (CC No Date): US 912122 (920709)
Applications (CC,No,Date): AU 9346675 (930707); WO 93US6404 (930707) Abstract (Basic): WO 9401576 A

A cDNA sequence encoding soluble foetal liver kinase-2 (*Flk*-*2*) is claimed. Also claimed are an expression cassette comprising a cDNA sequence encoding soluble *Flk*-*2* joined to and under the regulation of a transcriptional and translational regulatory region; and a vector comprises the expression cassette.

USE - The *Flk*-*2* proteins can be used in culture and in vivo for inhibiting binding of the

Flk-*2* *ligand* to *Flk*-*2* receptor. Thus, they can be used for modulating the growth of haematopoietic progenitor cells. The proteins can also be used for producing antibodies for identifying cells carrying *Flk*-*2*, removing soluble *Flk*-*2* from culture fluids or natural fluids, purifying *Flk*-*2* or assaying for the presence of *Flk*-*2*. Dwg.0/0

3/3,AB/48 (Item 5 from file: 351)
DIALOG(R)File 351:DERWENT WPI

009488944 WPI Acc No: 93-182479/22
Related WPI Accession(s): 92-366185; 93-036323; 93-405021; 95-005894 XRAM Acc No: C93-080827
Totipotent haematopoietic stem cell receptors, their ligands and DNA sequences - for treating anaemia(s) and bone marrow damage due to e.g. cancer chemotherapy or radiotherapy
Patent Assignee: (UYPR-) UNIV PRINCETON
Author (Inventor): LEMISCHKA I R
Patent Family:

CC Number	Kind	Date	Week	
WO 9310136	A1	930527	9322	(Basic)
AU 9331394	A	930615	9340	

Priority Data (CC No Date): US 793065 (911115)
Applications (CC,No,Date): WO 92US9893 (921116); AU 9331394 (921116) Abstract (Basic): WO 9310136 A

New isolated mammalian nucleic acid (I) encodes a receptor protein tyrosine kinase (II) expressed in primitive, but not mature, haematopoietic cells.

Also new are (1) vectors contg. (I) (2) isolated (II); (3) a *ligand* (L) that binds to (II) and stimulates proliferation and/or differentiation of primitive haematopoietic cells; (4) nucleic acid (Ia) encoding (L); (5) the murine cell line 2018 (ATCC CRL 10907); and (6) recombinant nucleic acid and isolated mRNA encoding (II) or fragments of it. Specifically (I) is cDNA or RNA and encodes human or murine fek(foetal liver kinase) -1 or murine *flk*-*2*. Full sequences, (3501, 3453 and 5406 bp) as reproduced in the specification together with the derived amino acid sequences.

(L) is a natural prod. (e.g. a growth factor, isolated or attached to cells), an antibody raised against (I) or against anti- *ligand* antibodies, or a non-protein cpd.

USE/ADVANTAGE - Treatment of stem cells, with (L) in vitro or in vivo, causes them to proliferate and/or differentiate i.e. they stimulate (1) self renewal of totipotent stem cells and (2) development of all cells in the haematopoietic system. The treatment is useful in cases of macrocytic aplastic anaemia and in bone marrow damage caused by chemotherapy or radiation Dwg.0/4

3/3,AB/49 (Item 6 from file: 351)
DIALOG(R)File 351:DERWENT WPI

009342859 WPI Acc No: 93-036323/04
Related WPI Accession(s): 92-366185; 93-182479; 93-405021; 95-005894 XRAM Acc No: C93-016479
Nucleic acid encoding receptor protein tyrosine kinase - allows development of ligands to stimulate proliferation and/or differentiation of mammalian haematopoietic stem cells Patent Assignee: (UYPR-) UNIV PRINCETON
Author (Inventor): LEMISCHKA I R
Patent Family:

CC Number Kind Date Week
WO 9300349 A1 930107 9304 (Basic)
AU 9222962 A 930125 9319
Priority Data (CC No Date): US 728913 (910628); US 793065 (911115); US 813593 (911224); WO 92US2750 (920402)
Applications (CC,No,Date): WO 92US5401 (920626); AU 9222962 (920626) Abstract (Basic): WO 9300349 A

The following are claimed.

(A) an isolated mammalian nucleic acid (NA) molecule (I) encoding a receptor protein tyrosine kinase (rpTK) expressed in primitive haematopoietic cells (pHC) and not expressed in mature haematopoietic cells (mHC), (B) isolated NA molecules that are flk-1 and/or *flk*-*2* (and comprise sequences given in the specification), (C) a vector comprising (I) as in (A) and/or comprising flk-1 or *flk*- *2*, (D) an isolated protein tyrosine kinase (pTK) as in (A), and/or which is flk-1, (E) a *ligand* (i) that binds to a rpTK and which stimulates the proliferation and/or differentiation of the primitive HCs, and (ii) that binds to the rpTK having the amino acid sequence of flk-1 or *flk*-*2*. The *ligand* stimulates proliferation and/or differentiation of cells that express flk-1 and/or *flk*-*2*, (F) a NA molecule encoding the *ligand* as in (E), (G) a method of stimulating the proliferation and/or differentiation of pHC stem cells comprising contacting the stem cells with a *ligand* that binds to the rpTK having the nucleic acid sequence of flk-1 or *flk*-*2*, and (H) an immune cell line 2018 having ATCC CRL 10907.

The NA molecule is cDNA or RNA. The NA is human or murine. The vector is capable of being cloned in a host pref. a prokaryotic or a ucaryotic host, and is capable of expressing the NA molecule in the host. Stimulation occurs in vitro or in vivo.

USE/ADVANTAGE - Using the methods and growth factors it is possible to exclusively stimulate stem cells without effecting mature cells Dwg.0/4

3/3,AB/50 (Item 7 from file: 351)
DIALOG(R)File 351:DERWENT WPI

009238764 WPI Acc No: 92-366185/44
Related WPI Accession(s): 93-036323; 93-182479; 93-405021; 95-005894 XRAM Acc No: C92-162604
Stimulating proliferation and/or differentiation of primitive mammalian haematopoietic stem cells - using *ligand* that binds thymidine kinase and flk-1 and *flk*-*2*
Patent Assignee: (UYPR-) UNIV PRINCETON
Author (Inventor): LEMISCHKA I R
Patent Family:
CC Number Kind Date Week
WO 9217486 A1 921015 9244 (Basic)
AU 9219248 A 921102 9305
US 5185438 A 930209 9308
EP 580760 A1 940202 9405
US 5283354 A 940201 9406
Priority Data (CC No Date): US 679666 (910402); US 728913 (910628); US 793065 (911115); US 813593 (911224)
Applications (CC,No,Date): WO 92US2750 (920402); AU 9219248 (920402); WO 92US2750 (920402); EP 92911275 (920402); WO 92US2750 (920402); US 679666 (910402); US 728913 (910628); US 793065 (911115); US 813593 (911224); US 946507 (920917)
Abstract (Basic): WO 9217486 A

Isolated mammalian nucleic acid (NA) molecule encodes a receptor protein thymidine kinase (TK) expressed in primitive but not in mature haematopoietic cells.

Also claimed are: (1) isolated NA that is *flk*-*2* comprising 3 defined sequences contg. e.g. 110 amino acids; (2) isolated NA which is flk-1 comprising a defined sequence contg. 1367 amino acids; (3) vectors comprising the above NAs; (4) isolated TK expressed in primitive but not mature haematopoietic cells; (5) a *ligand* that binds to this TK and to TKs flk-1 and *flk*-*2*, where the *ligand* stimulates the proliferation and/or differentiation of cells expressing the TKs; (6) a NA encoding the *ligand*; and (7) murine cell line 2018 (ATCC CRL 10907).

The NA is pref. DNA, cDNA or RNA, and is human or mouse. The vectors are transformed into pro- or eukaryotic cells. Stimulation of primitive haematopoietic stem cells occurs in vivo.

USE/ADVANTAGE - The proliferation and/or differentiation of primitive mammalian haematopoietic stem cells can be stimulated by contacting with the *ligand*. The ligands stimulate the proliferation of additional primitive stem cells and/or differentiation into more mature progenitor Dwg.0/4

Abstract (US): 9406 US 5283354 A

Recombinant nucleic acids (mRNA) that encode the prodn. of receptor protein tyrosine kinases (flk-1 and *flk*-*2* proteins); nucleic acid sequences that encode the formation of ligands for these receptors; and plasmids and expression vectors contg. these sequences are new.

Procaryotic and eucaryotic host cells have been transformed with these vectors and then propagated to produce the exogenous proteins. The nucleotide sequences and the aminoacid sequence of the proteins are defined.

USE/ADVANTAGE - The protein tyrosine kinases are haematopoietic growth factor receptors that stimulate the proliferation of totipotent haematopoietic stem and other cells, and the ligands also act as haematopoietic growth factors. Dwg.0/0 9308 US 5185438 A Mammalian nucleic acid that encodes the prodn. of receptor protein tyrosine kinases expressed in primitive hematopoietic cells but not in mature hematopoietic cells has been isolated.

The nucleotide sequence of the DNA and the aminoacid sequence of the protein have been defined in the specification. USE - The receptor protein are complexed with suitable ligands for the stimulation of primitive hematopoietic cell proliferation. Dwg. 0/0

? LOGOFF

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OneSearch, 3 files, 0.083 Hrs FileOS
$66.50 Estimated cost this search
$68.00 Estimated total session cost 0.166 Hrs.
Logoff: level 38.03.02 D 09:56:36